(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 July 2001 (19.07.2001)

PCT

(10) International Publication Number
WO 01/51440 A1

(51) International Patent Classification[7]: C07C 45/46, 45/00, 205/45, 49/84, C07B 41/06, C07D 295/18

(21) International Application Number: PCT/EP01/00047

(22) International Filing Date: 4 January 2001 (04.01.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/175,979 13 January 2000 (13.01.2000) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

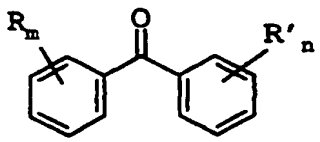
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/51440 A1

(54) Title: A PROCESS FOR THE PREPARATION OF SUBSTITUTED BENZOPHENONES



(I)

(57) Abstract: There is provided a process for the preparation of a compound of formula (I) via the acylation of the appropriate substituted benzene substrate in the presence of graphite and $FeCl_3$. Compounds of formula (I) are useful as intermediates in the manufacture of agrichemical agents.

A PROCESS FOR THE PREPARATION OF SUBSTITUTED BENZOPHENONES

Benzophenone compounds are key intermediates for highly active fungicidal and herbicidal agents. In particular, U.S. 4,912,217 describes the use of benzophenones as intermediates in the preparation of 3,3 diphenylacrylic acid amide fungicides. Said fungicides are especially useful for the control of phytopathogenic fungi. In addition, the use of certain benzophenone compounds as fungicidal agents has been disclosed in EP-A 897 904. Said benzophenone fungicides control ascomycetes in cereals, cucumber, apple or grape. Further, U.S. 5,484,763 and U.S. 5,523,278 describe the use of benzophenones as intermediates in the preparation of benzisoxazole and benzisothiazole herbicidal compounds. Therefore, the manufacture of these herbicidal and fungicidal agents in an economic environmentally safe, and ecologically sound manner is highly desirable.

Friedel-Crafts reactions (see Friedel Crafts and Related Reactions, G. Olah ed., Wiley-Interscience, New York, 1964) have been the primary means to prepare benzophenones. However, Said reaction requires the use of a strong Lewis Acid catalyst, especially aluminum chloride. Said catalysts generate large quantities of acid and toxic byproducts, which require neutralization and dilution prior to disposal. Such catalysts cannot be recycled, which adds to the cost of manufacture. A number of Friedel-Crafts catalysts other than aluminum chloride are also known, but most have similar drawbacks regarding the isolation of final product and recycling of catalyst. Recent publications have disclosed the use of graphite alone as a catalyst for a specific limited set of Friedel-Crafts acylations (M. Kodomari, J. Chem. Soc., Chem. Commun., 1997, 1567; Chemistry Letters, 1998, 319; Poster presentation, ICOS 12, Venice, July 1998 #PA 137). These publications disclose conditions which require benzene or chlorobenzene as solvent and significantly high loadings of graphite. Further, the published procedures are applicable to a limited variety of substituted benzophenone products and do not provide for ready access to the substituted benzophenones required for the manufacture of useful agrichemicals and agrichemical intermediates.

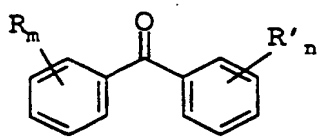
Therefore, it is an object of the present invention to provide an efficient preparation of a wide variety of substituted benzophenones with relatively low loadings of graphite/ferric chloride catalysts.

It is another object of this invention to provide an economic and environmentally safe source of a wide variety of commercially useful benzophenone intermediates and agrichemical products.

It is a feature of this invention that commercial production of benzophenone agrichemical agents and intermediates therefor may be accomplished without the requisite use of an acid chloride reagent.

Other objects and features of the invention will become more apparent from the detailed description set forth hereinbelow.

The present invention provides a process for the preparation of a benzophenone compound of formula I



(I)

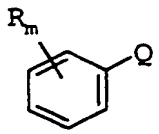
wherein m and n are each independently 0 or an integer of 1, 2, 3, 4 or 5;

R is halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxyalkyl, CO_2R_1, $S(O)_pR_2$, NR_3R_4, NO_2 or CN;

R' is C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_6alkoxyalkyl, or NR_5R_6;

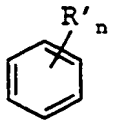
R_1, R_2, R_3, R_4, R_5 and R_6 are each independently C_1-C_6 alkyl; and

p is 0 or an integer of 1 or 2 which process comprises reacting a compound of formula II



(II)

wherein Q is CX_3 or COX; X is Cl or Br; and R and m are as described hereinabove with at least one molar equivalent of a compound of formula III



(III)

wherein R' and n are as described hereinabove in the presence of graphite in amounts of 1 g/mole to 20 g/mole of formula III and in the presence of $FeCl_3$, in an inert solvent, and when Q is CX_3 in the presence of at least one molar equivalent of water.

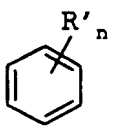
Also provided is the use of the formula I benzophenone compound in the commercial manufacture of an agrichemical agent.

Processes, to be useful an a manufacturing scale, preferentially contain key intermediate compounds which may be obtained in high to quantitative yield, which are stable either upon isolation or in situ and which may be produced from simple or readily available starting materials. Further, the most useful key intermediate compounds are those compounds which may be readily converted to the desired end product of manufacture in a minimum of reaction steps and with a minimum of undesirable side products in optimum yield and purity and, if applicable, regio- or stereospecifically.

The compounds of formula I are highly useful as fungicidal agents and as key intermediates in the manufacture of agrichemicals, such as 3,3 diphenylacrylic acid amide fungicides or benzisoxazole and benzisothiazole herbicides.

Advantageously, the process of the invention reduces the use of graphite/ferric chloride catalysts, eliminates the need for aluminum chloride catalysts and offers an alternative to the use of acid Chloride starting materials in the manufacture of key benzophenone compounds of formula I.

In accordance with the process of the invention, a compound of formula III

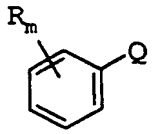


(III)

wherein n is 0 or an integer of 1, 2, 3, 4 or 5;

R' is C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxyalkyl, or NR_5R_6; and

R_5 and R_6 are each independently C_1-C_6 alkyl is acylated with a compound of formula II



(II)

wherein m is 0 or an integer of 1, 2, 3, 4 or 5;

R is halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6-alkoxy, C_1-C_6 alkoxyalkyl, CO_2R_1, $S(O)_pR_2$, NR_3R_4, NO_2 or CN;

Q is CX_3 or COX;

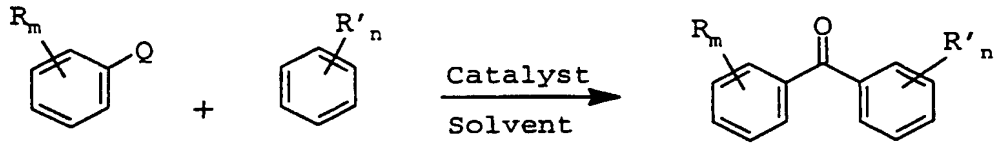
X is Cl or Br;

R_1, R_2, R_3 and R_4 are each independently C_1-C_6 alkyl; and

p is 0 or an integer of 1 or 2

in the presence of graphite in amounts of 1 g/mole to 20 g/mole of formula III and in the presence of $FeCl_3$, in an inert solvent, and when Q is CX_3 in the presence of at least one molar equivalent of water. The reaction sequence is shown in Flow Diagram I wherein the term catalyst designates graphite or a combination of graphite and $FeCl_3$.

Flow Diagram I



(II) (III) (I)

The term halogen as used in the specification and claims designates Cl, Br, F or I. The term haloalkyl designates and alkyl group C_nH_{2n+1} which is substituted with from 1 to 2n+1 halogen atoms which may be the same or different.

Solvents suitable for use in the process of the invention include halogenated aliphatic hydrocarbons such as dichloroethane, trichloroethane, tetrachloroethane or the like; aromatic hydrocar-

bons having one or more electron-withdrawing groups such as halobenzene, nitrobenzene, or the like; ethers such as dioxane, tetrahydrofuran, ethylene glycol or the like; or any conventional inert solvent which is incapable of participating in the reaction process, preferably halogenated aliphatic hydrocarbons or halogenated aromatic hydrocarbons, more preferably halogenated aliphatic hydrocarbons.

In the process of the invention the reaction rate is directly related to the reaction temperature, i.e. increased reaction temperatures lead to increased reaction rate. However, excessively high reaction temperatures may lead to an increase of undesired side products and decreased product yield and purity. In general, suitable reaction temperatures may range from about 25°C to 200°C, preferably about 50°C to 180°C.

Formula II compounds wherein Q is CX_3 are commercially available or may be obtained by conventional means, such as halogenation of the corresponding substituted toluene precursor with halogenating agents such as chlorine, bromine, N-bromosuccinamide, or N-chlorosuccinimide.

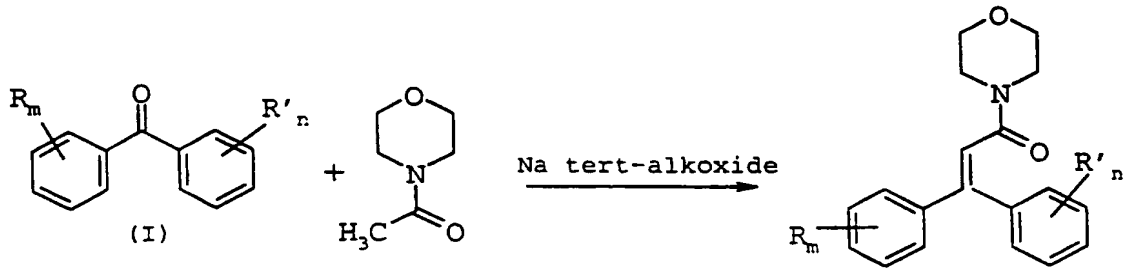
Similarly, formula II compounds wherein Q is COX are available commercially or may be obtained by conventional procedures such as hydrolysis of the corresponding benzotrihalide precursor, or by the reaction of the corresponding carboxylic acid precursor with oxychloride, phosphorous pentachloride, phosgene, thionyl chloride, or any of the conventional reagents used to convert a substituted benzoic acid to the corresponding benzoyl halide.

In actual practice, a compound of formula II is admixed with a compound of formula III (substrate) in the presence of an inert solvent, preferably a halogenated aliphatic hydrocarbon or a halogenated aromatic hydrocarbon, more preferably a halogenated aliphatic hydrocarbon, and graphite in amounts of 1g/mole of substrate to 20g/mole of substrate, preferably about 5g/mole to 10g/mole, in the presence of $FeCl_3$, preferably about 0.001 mole % to 1.0 mole %, more preferably about 0.05 mole % to 0.5 mole % and when the formula II compound is a compound wherein Q is CX_3, in the presence of at least one molar equivalent of water, preferably about 1 molar equivalent to 3 molar equivalents, at a temperature of about room temperature to the boiling point of the solvent, preferably about 25°C to 200°C, more preferably about 50°C to 180°C, to form the desired formula I benzophenone. The formula I product may be isolated using conventional methods such as filtration, extraction, chromatography or the like.

Advantageously, the process of the invention employs reaction conditions which are surprisingly mild, require a very low loading of catalyst and provide formula I benzophenone products in relatively high yield and purity with essentially no toxic waste products, as compared to the Standard Friedel-Crafts reaction conditions. Surprisingly, the process of the invention utilizes formula II compounds wherein Q is CX_3 to prepare benzophenone formula I compounds and thereby, offers an alternative to the use of an acid Chloride reagent to accomplish an effective and efficient acylation procedure.

Compounds of formula I are useful as fungicidal agents and as key intermediates in commercial chemical production, particularly agrichemical production. Accordingly, in one embodiment of the Invention the benzophenone compound of formula I prepared from the compounds of formula II and III as described hereinabove, may be reacted with N-acetylmorpholine in the presence of a sodium tert-alkoxide, optionally in the presence of a solvent, to give the fungicidal compound of formula IV. The reaction is illustrated in flow diagram II.

Flow Diagram II



(IV)

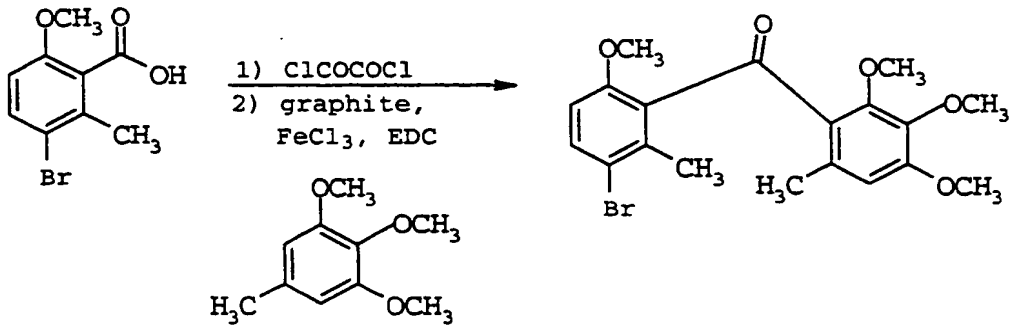
Reactions of substituted benzophenones to form diphenyl acrylic acid amide fungicides of formula IV are described in EP-A 897 904.

In order to provide a more clear understanding of the invention, the following examples are set forth below. The examples are merely illustrative and are not to be understood to limit the scope or underlying principles of the Invention in any way.

The terms ^{1}HNMR and ^{13}CNMR designate proton and carbon 13 NMR respectively. The terms HPLC, TLC and GLC designate high performance liquid chromatography, thin layer chromatography and gas-liquid chromatography, respectively. The term MS designates mass spectrum. Unless otherwise stated, all parts are parts by weight.

EXAMPLE 1 (According to the invention)

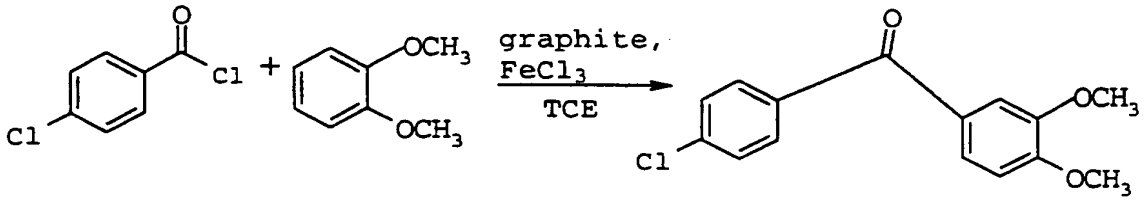
Preparation of 3'-Bromo-2,3,4,6'-tetramethoxy-2',6-dimethylbenzophenone



A slurry of 3-bromo-6-methoxy-2-methylbenzoic acid (7.35 g, 0.03 mol) in 1,2-dichloroethane (EDC) is treated with oxalyl Chloride (4.18 g, 0.033 mol) at room temperature over a 15 minute period, heated to 70°C for 2 hours, cooled to room temperature, treated with 3,4,5-trimethoxytoluene (5.5 g, 0.03 mol), anhydrous $FeCl_3$ (16 mg, 0.33 mol%), and graphite (250 mg), heated at reflux temperature for 3 hours (reaction complete by GLC analysis) and filtered. The filtrate is washed with saturated $NaHCO_3$ solution and concentrated in vacuo to give a residue. The residue is triturated with 15% ethyl acetate/heptane to give the title product as a pale gray solid, 8.8 g, 71.7% yield, mp 96°-97°C.

EXAMPLE 2 (According to the invention)

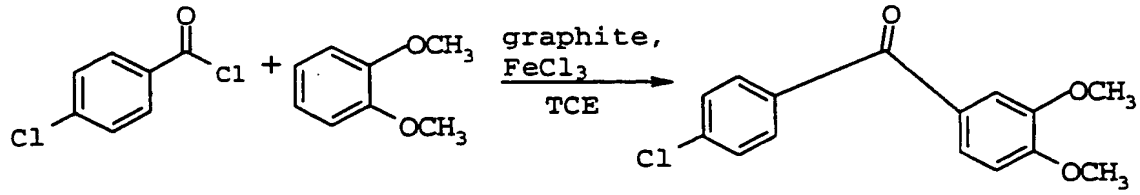
Preparation of 4'-Chloro-3,4-dimethoxybenzophenone



A slurry of p-chlorobenzoyl chloride (5.25 g, 0.03 mol), veratrole (4.56 g, 0.033 mol), anhydrous $FeCl_3$ (16 mg, 0.33 mol%) and graphite (250 mg) in TCE is heated at reflux temperature for 3 hours, cooled to room temperature and filtered. The filtrate is washed with saturated $NaHCO_3$ solution and concentrated in vacuo to give an oil residue. The residue is triturated with 15% ethyl acetate/heptane to give the title product as a white solid, 7.0 g 84.3% yield, mp 110°-112°C.

EXAMPLE 3 (According to the invention)

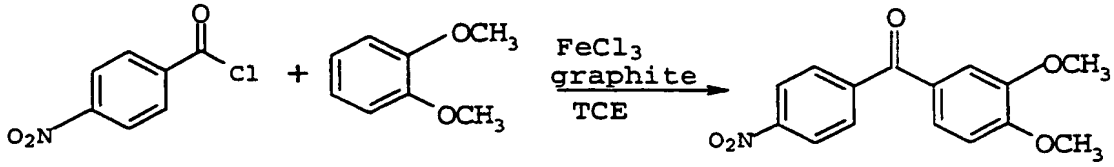
Preparation of 4'-Chloro-3,4-dimethoxybenzophenone



A slurry of p-chlorobenzoyl chloride (5.25 g, 0.03 mol), veratrole (4.56 g, 0.033 mol), $FeCl_3$ (8 mg, 0.16 mol%) and graphite (250 mg) in TCE is heated at reflux temperature for 8 hours and filtered. The filtrate is washed with saturated $NaHCO_3$ solution and concentrated in vacuo to give an oil residue. The residue is triturated with 15% ethyl acetate/heptane to give the title product as a white solid, 7.0 g, 84.3% yield mp 110.5° -111.5°C.

EXAMPLE 4 (According to the invention)

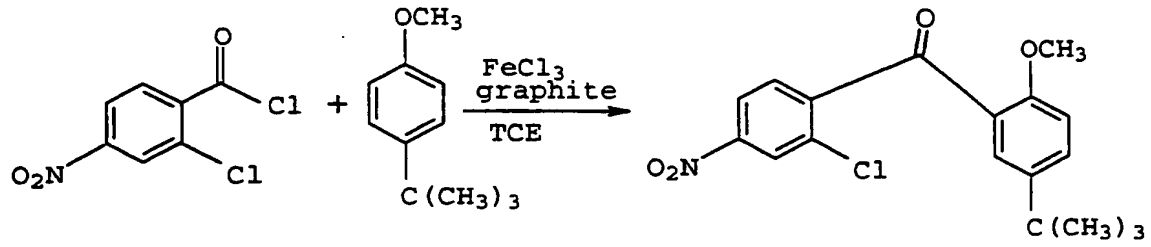
Preparation of 3,4-Dimethoxy-4'-nitrobenzophenone



A slurry of p-nitrobenzoyl Chloride (5.57 g, 0.03 mol), veratrole (4.15 g, 0.03 mol), anhydrous $FeCl_3$ (16 mg, 0.33 mol%), and graphite (250 mg) in TCE is heated at reflux temperature for 20 hours, cooled to room temperature and filtered. The filtrate is washed with saturated $NaHCO_3$ solution and concentrated in vacuo to give an oil residue. The residue is triturated with 15% ethyl acetate/heptane to give a yellow solid. The solid is dispersed in ethyl acetate, heated at reflux temperature for 15 min., cooled and filtered to give the title product as a yellow solid, 5.3g, 61.5 yield, mp 162°-167°C.

EXAMPLE 5 (According to the invention)

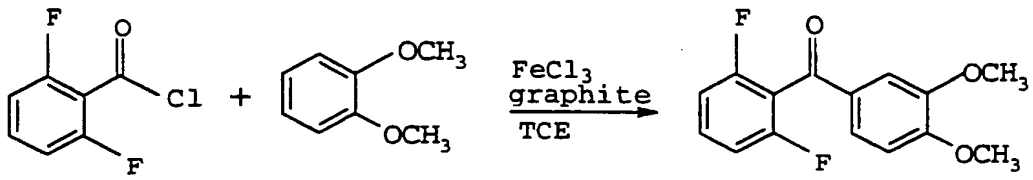
Preparation of 5-tert-Butyl-2'-chloro-2-methoxy-4'nitrobenzophenone



A mixture of 2-chloro-4-nitrobenzoyl Chloride (7.92 g, 0.036 mol), p-tert-butylanisole (4.93 g, 0.03 mol), anhydrous $FeCl_3$ (16 mg, 0.33 mol%) and graphite (250 mg) in TCE is heated at reflux temperature for 2 hours, cooled to room temperature and filtered. The filtercake is washed with TCE. The combined filtrates are washed with saturated $NaHCO_3$ solution and concentrated in vacuo to give an oil residue. The residue is purified by flash column chromatography an silica gel, packed and eluted with 15 % ethyl acetate/heptane, and by crystallization from 5% ethyl acetate/heptane to give the title product as a white solid, 5.7 g, 54.6% yield, mp 82.5°-83.5°C characterized by ^{1}HNMR and MS analyses.

EXAMPLE 6 (According to the invention)

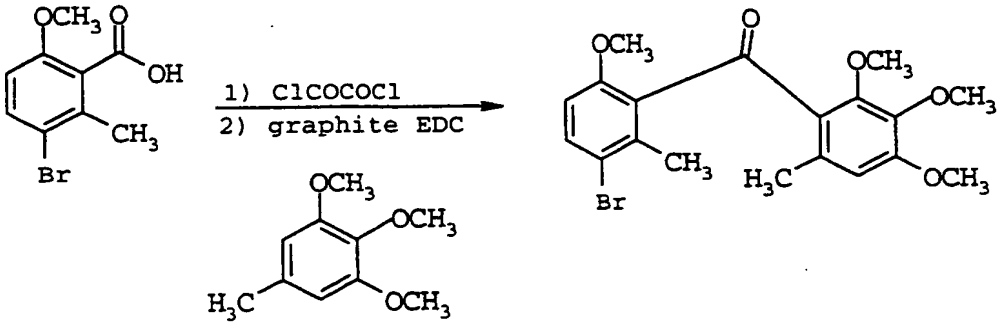
Preparation of 2',6'-Difluoro-3,4-dimethoxybenzophenone



A slurry of 2,6-difluorobenzoyl Chloride (5.3 g, 0.03 mol), veratrole (4.15 g, 0.03 mol), anhydrous $FeCl_3$ (16 mg, 0.33 mol%), and graphite (250 mg) in TCE is heated at reflux temperature for 2.5 hours, cooled to room temperature and filtered. The filtrate is washed with saturated $NaHCO_3$ solution and concentrated in vacuo to give an oil residue. The residue is triturated with 15 % ethyl acetate/heptane to give a brown solid. The solid is crystallized from 15 % ethyl acetate/heptane to give the title product as a pale yellow solid, 3.9 g, 46.7% yield, mp 100°-101°C.

EXAMPLE 7 (Comparative Example)

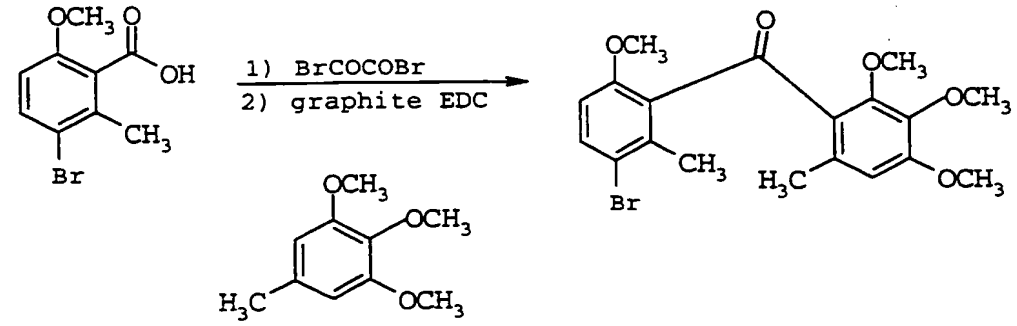
Preparation of 3'-Bromo-2,3,4,6'-tetramethoxy-2',6-dimethylbenzophenone



A slurry of 3-bromo-6-methoxy-2-methylbenzoic acid, (4.9 g, 0.02 mol) in 1,2-dichloroethane (EDC) is treated with oxalyl Chloride (2.7 g, 0.022 mol) at room temperature over a 15 minute period, heated to 60°C for 30 minutes, cooled to room temperature, treated with 3,4,5-trimethoxytoluene (2.73 g, 0.015 mol) and graphite (1.0 g), heated at reflux temperature for 2.5 hours [reaction is complete by TLC (silica gel, 25% ethyl acetate/ heptane)], cooled to room temperature, and filtered. The filtrate is washed with saturated NaHC03 solution and concentrated in vacuo to give a residue. The residue is triturated with 15% ethyl acetate/heptane to give the title product as a white solid, 4.25 g, 69.2 yield, mp 96°-97°C, characterized by ^{1}HNMR and MS analyses.

EXAMPLE 8 (Comparative Example)

Preparation of 3'-Bromo-2,3,4,6'-tetramethoxy2',6-dimethylbenzophenone

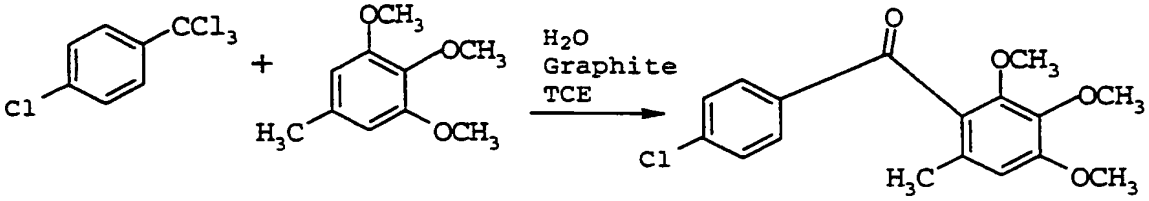


A slurry of 3-bromo-6-methoxy-2-methylbenzoic acid (4.9 g, 0.02 mol) in 1,2-dichloroethane (EDC) is treated with oxalyl bromide (4.75 g, 0.022 mol) at room temperature over a 15 minute period, heated to 50°C for 2 hours, cooled to room temperature and concentrated in vacuo to give the corresponding acid bromide. This Grude acid bromide is dissolved in EDC, treated with

3,4,5-trimethoxytoluene (1.82 g, 0.01 mol) and graphite (1.0g), heated at reflux temperature for 3 hours [reaction is complete by TLC (silica gel, 25% ethyl acetate/ heptane)], cooled to room temperature and filtered. The filtrate is washed with saturated $NaHCO_3$ solution and concentrated in vacuo to give a brown oil residue. The residue is purified by flash column chromatography an silica gel, packed and eluted with 15% ethyl acetate/heptane, to give the title product as a white crystalline solid, 2.2 g, 53.8 yield, mp 97°-98°C, characterized by ^{1}HNMR and MS analyses.

EXAMPLE 9 (Comparative Example)

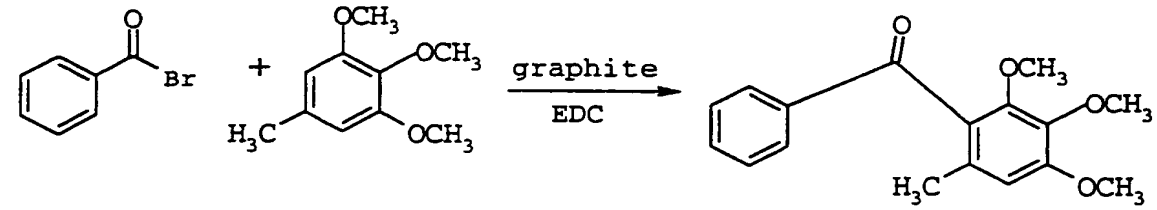
Preparation of 4'-Chloro-2,3,4-trimethoxy-5-methylbenzophenone



A mixture of p-chlorobenzotrichloride (6.9 g, 0.03 mol), 3,4,5-trimethoxytoluene (6.6 g, 0.036 mol), and graphite (1.5 g) in 1,1,2,2 tetrachloroethane (TCE) is heated to 100°C, treated with water (0.6 g, 0.036 mol), heated to reflux temperature for 1.5 hours, treated with additional water (0.48 g, 0.026 mol), heated for another 2.5 hours at reflux temperature, cooled to room temperature and filtered. The filtrate is washed with aqueous $NaHCO_3$ solution and concentrated in vacuo to give an oil residue. The residue which is purified by flash column chromatography an silica gel, packed and eluted with 15% ethyl acetate/ heptane, to give the title product as a white crystalline solid, 6.2 g, 64.4% yield, mp 99.5°-100.0°C, characterized by ^{1}HNMR and MS analyses.

EXAMPLE 10 (Comparative Example)

Preparation of 2,3,4-Trimethoxy-6-methyl-benzophenone

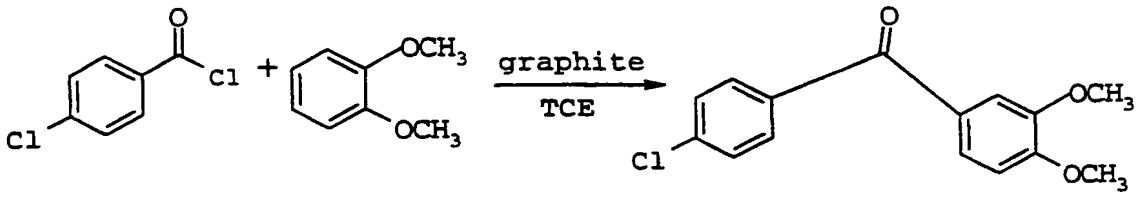


A mixture of benzoyl bromide (2.8 g, 0.015 mol), 3,4,5-trimethoxytoluene (1.8 g, 0.01 mol) and graphite (1.0 g) in 1,2-dichloroethane (EDC) is heated at reflux temperature for 9 hours, cooled to room temperature and filtered. The filtrate is washed with saturated $NaHC0_3$ solution and concentrated *in vacuo* to give a re-

sidue. The residue is triturated with 15% ethyl acetate/heptane to give the title product as a pale yellow solid, 1.2 g, 42% yield, mp 88°-89°C, characterized by ^{1}HNMR and MS analyses.

EXAMPLE 11 (Comparative Example)

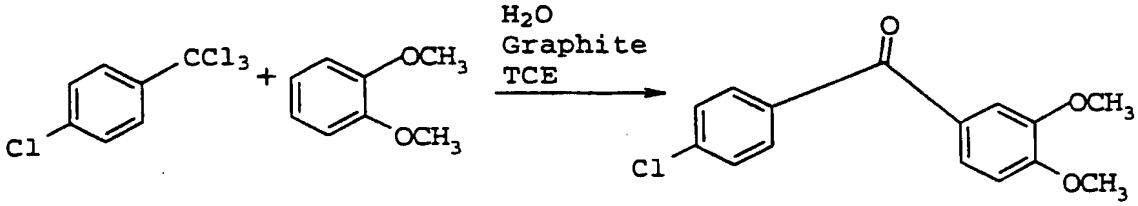
Preparation of 4'-Chloro-3,4-dimethoxybenzophenone



A slurry of p-chlorobenzoyl chloride (5.25 g, 0.03 mol), veratrole (4.15 g, 0.03 mol) and graphite (1.5 g) in TCE is heated at reflux temperature for 8 hours, cooled to room temperature and filtered. The filtrate is washed with saturated $NaHC0_3$ solution and concentrated *in* vacuo to give an oil residue. The residue is triturated with 15% ethyl acetate/heptane to give the title product as a pale yellow solid, 6.75 g, 81.3 yield, mp 110°-112°C, characterized by ^{1}HNMR analysis.

EXAMPLE 12 (Comparative Example)

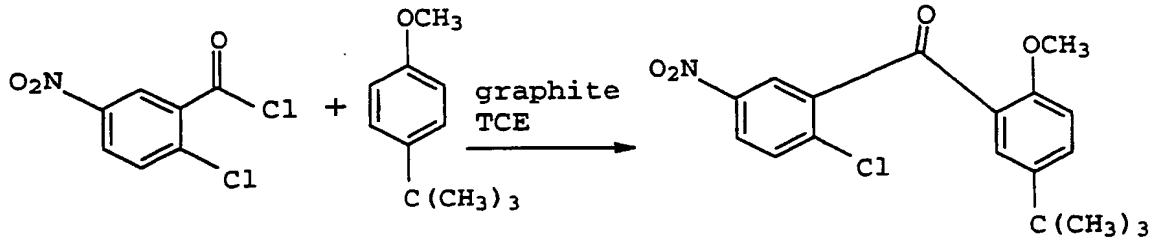
Preparation of 4'-Chloro-3,4-dimethoxybenzophenone



A mixture of p-chlorobenzotrichloride (6.9 g, 0.03 mol), veratrole (5.0 g, 0.036 mol), and graphite (1.0 g) in TCE is heated to 100°C, treated with water (0.6 g, 0.036 mol), heated to reflux temperature for 1.5 hours, treated with additional water (0.036 g, 0.02 mol) heated at reflux temperature for 4.5 hours, cooled to room temperature and filtered. The filtrate is washed with aqueous $NaHCO_3$ solution and concentrated in vacuo to give an oil residue. The residue is triturated with 15% ethyl acetate/heptane to give the title product as a white solid, 6.6 g, 79.5% yield, mp 110°-112°C.

EXAMPLE 13 (Comparative Example)

Preparation of 5-tert-Butyl-2'-chloro-2-methoxy-5'-nitrobenzophenone

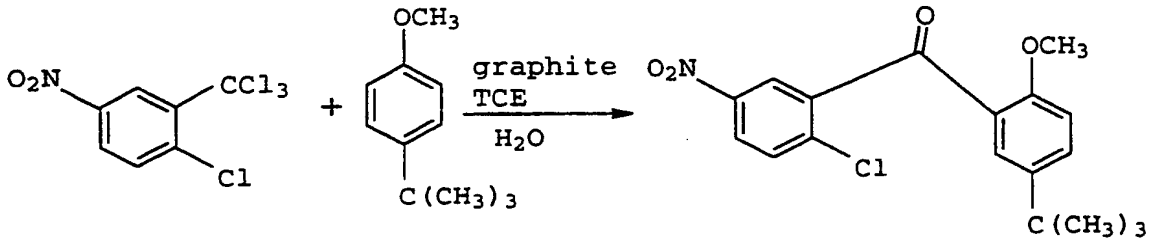


A slurry of 2-chloro-5-nitrobenzoyl chloride (2.2 g, 0.01 mol), p-tert-butylanisole (1.65 g, 0.01 mol), and graphite (0.5 g) in TCE is heated at reflux temperature for 2.5 hours, cooled to room temperature and filtered. The filtrate is washed with saturated $NaHCO_3$ solution and concentrated in vacuo to give an oil residue. The residue is triturated with 15% ethyl acetate/heptane to give the title product as a white solid, 2.0 g, 57.6 yield, mp 136°-139°C, characterized by ^{1}HNMR and MS analyses.

Using essentially the same procedure described hereinabove and substituting 1,2-dichloroethane as solvent, the title product is obtained as a white solid in 79.6% yield, mp 136°-139°C.

EXAMPLE 14 (Comparative Example)

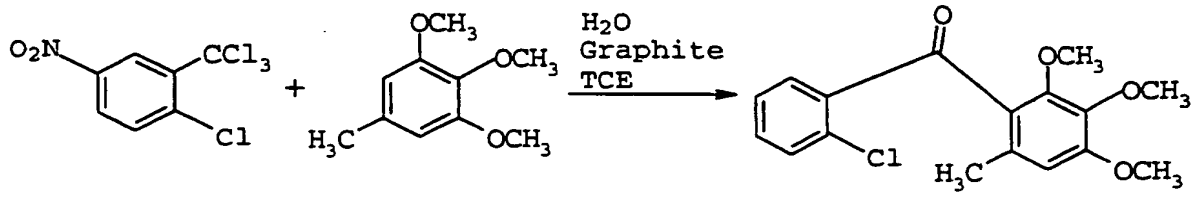
Preparation of 5-tert-Butyl-2'-chloro-2-methoxy-5'-nitrobenzophenone



A mixture of 2-chloro-5-nitrobenzotrichloride, 2.75 g, 0.01 mol), ptert-butylanisole (1.65g, 0.01 mol), and graphite (0.5 g) in TCE is heated to 100°C, treated with water (0.2 g, 0.011 mol), heated to reflux temperature for 2 hours, treated with additional water (0.2 g, 0.011 mol), heated at reflux temperature for 4 hours, cooled to room temperature and filtered. The filtrate is washed with aqueous $NaHCO_3$ solution and concentrated in vacuo to give an oil residue. The residue is triturated with 15 % ethyl acetate/ heptane to give the title product as a white solid, 1.75 g, 50.4% yield, characterized by TLC and ^{1}HNMR analyses.

EXAMPLE 15 (Comparative Example)

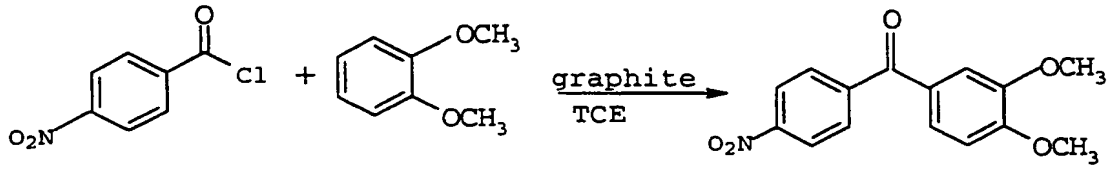
Preparation of 2'-Chloro-2,3,4-trimethoxy-5-methyl-5'-nitrobenzophenone



A mixture of 2-chloro-5-nitrobenzotrichloride (5.5 g, 0.02 mol), 3,4,5-trimethoxytoluene (3.658, 0.02 mol), and graphite (1.5 g) in TCE is heated to 100°C, treated with water (0.368, 0.02 mol), heated at reflux temperature for 2 hours, treated with additional water (0.36g, 0.02 mol) and heated at reflux temperature for 3 hours, cooled to room temperature and filtered. The filtrate is washed with aqueous $NaHC0_3$ solution and concentrated in vacuo to give an oil residue. The residue is purified by flash column chromatography an silica gel, packed and eluted with 15 % ethyl acetate/heptane to give the title product as an oil which solidified an standing, 1.4 g, 19 % yield, characterized by ^{1}HNMR and MS analyses.

EXAMPLE 16 (Comparative Example)

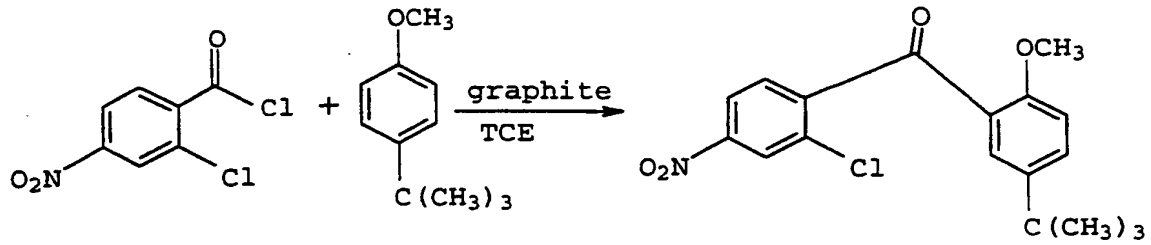
Preparation of 3,4-Dimethoxy-4'-nitrobenzophenone



A slurry of p-nitrobenzoyl Chloride (5.57 g, 0.03 mol), veratrole (4.15 g, 0.03 mol), and graphite (1.5 g) in TCE is heated at reflux temperature for 20 hours, cooled to room temperature and filtered. The filtrate is washed with saturated $NaHCO_3$ solution and concentrated in vacuo to give an oil residue. The residue is triturated with 15 % ethyl acetate/heptane to give a yellow solid. The solid is mixed with 15% ethyl acetate in hexane and heated at reflux temperature for 15 min., cooled and filtered to give the title product as a yellow solid, 4.4g, 51 % yield, mp 160°-162°C.

EXAMPLE 17 (Comparative Example)

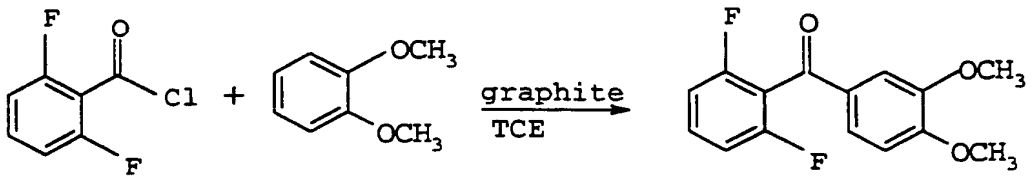
Preparation of 5-tert-Butyl-2'-chloro-2-methoxy-4'-nitrobenzophenone



A mixture of 2-chloro-4-nitrobenzoyl chloride (7.92 g, 0.036 mol), p-tert-butylanisole (4.93 g, 0.03 mol), and graphite (1.0 g) TCE is heated at reflux temperature for 5 hours, cooled to room temperature and filtered. The filtercake is washed with TCE. The combined filtrates are washed with saturated $NaHCO_3$ solution and concentrated in vacuo to give an oil residue. The residue is purified by flash column chromatography an silica gel, packed and eluted with 15% ethylacetate/heptane and by crystallization from 5% ethyl acetate/heptane, to give the title product as a white solid, 5.83g, 55,9 % yield, mp 84°-85°C, characterized by ^{1}HNMR and MS analyses.

EXAMPLE 18 (Comparative Example)

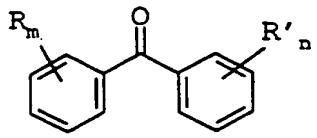
Preparation of 2',6'-Difluoro-3,4-dimethoxybenzophenone



A slurry of 2,6-difluorobenzoyl chloride (5.3 g, 0.03 mol), veratrole (4.15 g, 0.03 mol), and graphite (1.5 g) in TCE is heated at reflux temperature for 1.5 hours, cooled to room temperature and filtered. The filtrate is washed with saturated $NaHCO_3$ solution and concentrated in vacuo to give an oil residue. The residue is triturated with 15% ethyl acetate/heptane to give the title product as a white solid, 6.7 g, 77.7% yield, mp 100.5°-101.0°C.

CLAIMS:

1. A process for the preparation of a compound of formula I



(I)

wherein m and n are each independently 0 or an integer of 1, 2, 3, 4 or 5;

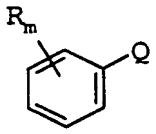
R is halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxyalkyl, CO_2R_1, $S(O)_pR_2$, NR_3R_4, NO_2 or CN;

R' is C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxyalkyl, or NR_5R_6;

R_1, R_2, R_3, R_4, R_5 and R_6 are each independently C_1-C_6 alkyl; and

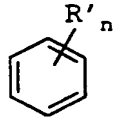
p is 0 or an integer of 1 or 2;

which process comprises reacting a compound of formula II



(II)

wherein Q is CX_3 or COX; X is Cl or Br; and R and m are as described hereinabove with at least one molar equivalent of a compound of formula III



(III)

wherein R' and n are as described hereinabove

in the presence of graphite in amounts of 1 g/mole to 20 g/mole of formula III and in the presence of $FeCl_3$, in an inert solvent, and when Q is CX_3 in the presence of at least one molar equivalent of water.

2. The process according to Claim 1 wherein the solvent is a halogenated aliphatic hydrocarbon or a halogenated aromatic hydrocarbon.

3. The process according to Claim 2 wherein the solvent is a halogenated aliphatic hydrocarbon.

4. The process according to Claim 1 having a formula II compound wherein Q is COX.

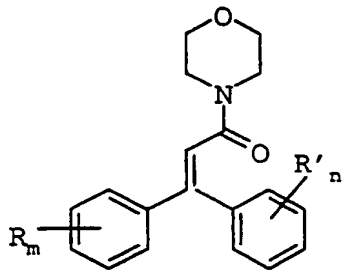
5. The process according to Claim 1 having a formula II compound wherein Q is CX_3.

6. The process according to Claim 1 wherein the graphite is present at 5 g/mole of formula III to 10 g/mole of formula III.

7. The process according to Claim 1 wherein the $FeCl_3$ is present at 0.001 mole% to 1.0 mole%.

8. The process according to Claim 5 wherein water is present at 1.0 molar equivalent to 3 molar equivalents.

9. A process according to claim 1 for the preparation of a compound of formula IV



(IV)

wherein the variables and the indices are as defined for formula I in claim 1, and reacting said formula I compound with N-acetylmorpholine in the presence of sodium tert-alkoxide, optionally in the presence of a solvent, to give the desired formula IV product.

INTERNATIONAL SEARCH REPORT

Interna[redacted] Application No
PCT/EP 01/00047

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C45/46 C07C45/00 C07C205/45 C07C49/84 C07B41/06
C07D295/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07B C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal, BEILSTEIN Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 125, no. 11, 9 September 1996 (1996-09-09) Columbus, Ohio, US; abstract no. 142197, GOENDOES, GY. ET AL: "Friedel-Crafts reaction with FeCl3-graphite" XP000664270 abstract & J. PHYS. CHEM. SOLIDS (1996), 57(6-8, PROCEEDINGS OF THE 8TH INTERNATIONAL SYMPOSIUM ON INTERCALATION COMPOUNDS, 1995), 855-857 , --- -/--	1

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 May 2001	30/05/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bonnevalle, E

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	KODOMARI, MITSUO ET AL: "Graphite as an effective catalyst for Friedel-Crafts acylation" CHEM. COMMUN. (CAMBRIDGE) (1997), (16), 1567-1568 , XP002166560 cited in the application the whole document	1-4
Y	EP 0 854 128 A (AMERICAN CYANAMID CO) 22 July 1998 (1998-07-22) page 5, line 5 - line 10	1-4
A	KHADILKAR, BHUSHAN M. ET AL: "Synthesis of benzophenones using silica-gel supported Lewis acid catalyst" TETRAHEDRON LETT. (1997), 38(9), 1641-1642 , XP000644228 the whole document	1,5

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 01/00047

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0854128 A	22-07-1998	BR 9800281 A	08-09-1999
		JP 10204020 A	04-08-1998